Brinson, 1:12
http://dx.doi.org/10.4172/scientificreports.542

Open Access Scientific Reports

Review Article Open Access

Potential Implications of Baseline Viral Load on the Relative Potency of First-line, NNRTI-Based Antiretroviral Therapy

Cynthia Brinson*

Central Texas Clinical Research, Austin, USA

Abstract

High baseline viral loads (>100,000 copies/ml) have been associated with reduced virologic efficacy and safety, and can indicate greater viral replication and/or advanced disease. The latest DHHS guidelines recommend that abacavir- and rilpivirine-based regimens should be used with caution in patients with high viral loads (>100,000 copies/ml). NNRTI-based ARV regimens generally have fewer concerns regarding virologic efficacy and safety in patients with high viral loads. An extended-release formulation of the NNRTI nevirapine allows for once-daily dosing. This treatment schedule has been associated with greater regimen adherence and improved patient outcomes. Regimen responses to baseline HIV viral loads are among the various patient and viral factors that need to be considered during regimen selection and treatment optimization.

Keywords: Viral load; Antiretroviral therapy; Non Nucleoside Reverse Transcriptase inhibitor

Introduction

For some antiretroviral (ARV) therapies, patient baseline viral load (VL) has been predictive of relative potency in terms of the regimen achieving sustained virologic suppression. Reports from several randomized clinical trials of certain agents have described apparent differences in virologic efficacy and safety profiles, depending on patient stratification by baseline VL, generally <100,000 copies/ml versus ≥ 100,000 copies/ml. The latter is generally associated with higher levels of viral replication and, in some cases, more advanced disease or likelihood of disease progression [1]. These differences vary according to the study drug, as this trend has not been observed universally. Indeed some agents, such as the recently approved Non Nucleoside Reverse Transcriptase inhibitor (NNRTI) rilpivirine (RPV), have product labeling indicating that they should be used with caution in patients with high baseline VLs [2].

Even if not directly translated into therapeutic precautions, a trend of decreased efficacy among patients with high baseline VLs has been noted for some ARV agents. In a post-hoc analysis of potential baseline predictors of first-line therapy outcomes among treatment-naïve patients receiving either efavirenz (EFV) or nevirapine (NVP) on a background of stavudine (d4T) and lamivudine (3TC), van Leth et al. [3] reported an increased risk of virologic failure when VL was ≥ 100,000 copies/ml (hazard ratio [HR] 1.20, confidence interval [CI] 0.96-1.50). The ACTG 5202 trial [4], a randomized, controlled study in >1,800 treatment-naive patients, compared four once-daily ARV regimens as initial therapy: either ritonavir-boosted atazanavir (ATV/r) or EFV with a background of abacavir (ABC)/3TC or tenofovir (TDF)/emtricitabine (FTC). The primary efficacy endpoint was the time to virologic failure (confirmed VL ≥ 1,000 copies/ml) at 16 through 24 weeks or ≥ 200 copies/ml at or after 24 weeks. During an interim review, significant differences in virologic efficacy were seen among patients with screening VL ≥ 100,000 copies/ml. With a median follow-up of 60 weeks, the time to virologic failure was significantly shorter in the ABC/3TC groups than in the TDF/FTC groups among patients with a screening VL of ≥ 100,000 copies/ml (HR 2.33, 95% CI 1.46-3.72; P<0.001) [4]. Also, reported virologic failures were more common in the ABC/3TC groups (n=57, 14%) compared with the TDF/FTC groups (n=26, 7%). The time to the first adverse event was also shorter in the ABC/3TC groups (P<0.001). Interestingly, no significant between-group difference was observed for change in CD4+ T-cell count from baseline to week 48 [4].

In contrast, the HEAT study, a subgroup analysis of virologic efficacy according to baseline VLs <100,000 copies/ml versus ≥ 100,000 copies/ml, reported that similar percentages of participants were virologically suppressed (HIV RNA <50 copies/ml) at 96 weeks in patients receiving either ABC/3TC or TDF/FTC in combination with once-daily LPV/r (63% *vs.* 58% in those with <100,000 copies/ml and 56% *vs.* 58% in those with ≥ 100,000 copies/mL, respectively) [5]. On the other hand, a sub-analysis of recent data from the EuroSIDA study group of etravarine-based ARV regimens, indicates that after adjusting for virologic genotype, per log10 increases in baseline VLs do not seem to confer an increase in risk of on-treatment virologic failure (relative hazard 1.20, 95% CI = 0.87-1.65; P=0.258) [6].

A similar impact of baseline VL on ARV efficacy has been seen with other ARV drug classes. For example, in the recent ACTG A5262 study, 112 treatment-naïve patients received darunavir (DRV)/r 800/100 mg once daily and raltegravir (RAL) 400 mg twice daily in a single arm study assessing virologic failure at week 24 of treatment. In these patients, virologic failure was associated with baseline VL ≥ 100,000 copies/ml (HR 3.76, 95% CI 1.52-9.31; P=0.004) and lower baseline CD4+ T-cell count (0.77 per 100 cells/μl increase [95% CI 0.61-0.98]; P=0.037), after adjusting for age and gender [7].

Results from these and other studies that are underway indicate that clinicians must consider a number of patient and viral factors when deciding on treatment regimens, especially in patients with high baseline VLs [8].

Once-daily versus Twice-daily Formulations of NVP: Insights from Baseline Viral Load Subgroup Analysis in the VERxVE Trial

VERxVE was a double-blind, double-dummy trial comparing the

***Corresponding author:** Cynthia Brinson, MD, Central Texas Clinical Research, 900 East 30th Suite 302, Austin, TX 78751, USA, E-mail: cbrinson@ctcrcorp.com

Received March 15, 2012; **Published** November 30, 2012

Citation: Brinson C (2012) Potential Implications of Baseline Viral Load on the Relative Potency of First-line, NNRTI-Based Antiretroviral Therapy. 1:542 doi:10.4172/scientificreports.542

efficacy and safety of the original immediate-release (IR) and recently approved extended-release (XR) formulations of NVP in first-line therapy for treatment-naïve, HIV-infected patients (n=1,011) [9]. After a 14-day lead-in period of NVP IR treatment administered to all patients, participants were stratified by baseline VL (<100,000 *vs.* ≥ 100,000 copies/ml) with randomization (1:1) to NVP XR (400 mg once daily) plus placebo or NVP IR (200 mg twice daily) plus placebo, both on a background of TDF/FTC (once daily) for 48 weeks [9]. The primary endpoint was sustained virologic response through week 48, defined as two consecutive VL measures <50 copies/ml (at least 2 weeks apart), with no subsequent viral rebound or change in ARV therapy, according to the US Food and Drug Administration (FDA) time to loss of virologic response (TLOVR) algorithm [9].

The week-48 subgroup analyses showed that patients with lower VLs demonstrated proportionally higher virologic responses. Thus, among patients with baseline VLs ≤ 100,000 copies/ml, the virologic efficacy rates of the two formulations were similar: 85.9% (267/311) of patients treated with NVP XR and 79.2% (240/303) treated with NVP IR. In patients with higher baseline VL, the two NVP formulations also demonstrated similar virologic efficacy: 73.2% (142/194) of patients treated with NVP XR and 70.9% (144/203) of those treated with NVP IR.

However, the TLOVR rates were lower overall in the group with high VLs compared with those with lower VL [9].

These recent data are consistent with the previously observed associations between baseline VL and HIV therapeutic potency. Although the somewhat lower NVP efficacy rates seen among patients with high baseline VL are likely not substantial enough to consider cautionary prescribing language, this serves as another example to reinforce the importance of baseline VL levels when constructing ARV therapy regimens. Clinicians considering optimal ARV regimens should take baseline VL into consideration, along with various other patient and viral factors, such as treatment and disease history, resistance-testing results, regimen tolerability issues, and accompanying comorbidities.

Fixed-dose NNRTI Combinations: Recent Data on Rilpivirine or Efavirenz

The recent FDA approval of Complera™ (Gilead Sciences, Inc, Foster, CA, USA), a fixed-dose combination of RPV with TDF and FTC, allows the convenience of once-daily, single-tablet dosing in a NNRTI-based regimen [10]. However, pooled virologic 48-week outcome data from the C209 and C215 randomized studies indicate that patients receiving either RPV or EFV in combination with TDF/FTC have a progressively greater probability of virologic failure at week 48 (according to baseline VL stratification) [10].

Specifically, RPV-based regimens demonstrated an approximate twofold increase in virologic failure compared with EFV-based regimens in each baseline VL stratification category (Table 1) [10]. A larger proportion of RPV-treated patients with baseline VL ≥ 100,000 copies/ml experienced virologic failure compared with patients with baseline VL <100,000 copies/ml [2]. This virologic failure was associated with higher rates of treatment resistance and cross-resistance to other members of the NNRTI class than previously reported with EFV [2].

NNRTIs as Once-daily Options for Initial ARV Therapy

Fixed-dose combination ARV regimens have continued to evolve into one pill taken once daily, and a number of novel combinations are currently in development. A key motivation for the development of these once-daily formulations is that treatment simplification has been associated with better patient adherence, especially in difficult-to-treat populations such as the homeless and the marginally housed [11].

NNRTI agents have a number of pharmacodynamic and chemical (lipophylic) properties that make them potentially desirable components of ARV regimens for the long-term management of HIV infection. These properties include the ability to permeate cellular membranes and achieve high intracellular concentrations, along with good penetration into multiple body compartments such as the central nervous system and across the placenta [12].

Also, the long functional half-lives of these agents contribute to better chances for improved virologic control in the setting of combination therapy [12].

Considerations Regarding the Use of Older Versus Newer NNRTIs

According to the US Department of Health and Human Services (DHHS) HIV treatment guidelines, EFV is the preferred NNRTI component of ARV regimens for treatment-naïve patients, based on numerous comparative clinical trials and years of patient experience [8]. All NVP-based regimens are now considered to be acceptable treatment [8]. NVP is widely used around the world, and has accrued more than a million patient-years of experience [12]. This extensive experience is the foundation for a well understood NVP safety profile [13], including current treatment-initiation guidelines based on CD4+ T-cell count in patients starting NVP treatment [12]. The adoption of these recommendations has reduced the overall incidence of NVP-associated rash and hepatoxicity to levels comparable to that seen with other ARV drugs [14].

Newer agents, such as RPV [2] and the related fixed-dose

Baseline viral load (copies/ml)	RPV+TDF/FTC (n=550)	EFV+TDF/FTC (n=546)
≤ 100,000	5%	3%
>100,000 to ≤ 500,000	20%	11%
>500,000	30%	18%

EFV: efavirenz; RPV: rilpivirine; TDF/FTC: tenofovir/emtricitabine
[a]Analysis includes subjects with viral load ≥ 50 copies/ml during the week-48 window (weeks 44–54) by intent-to-treat analysis

Table 1: Virologic Failurea by Baseline Viral Load (copies/ml).

NNRTI-based Regimen	Baseline HIV RNA >100,000 copies/mL: regimen a consideration?
EFV/TDF/FTC	No
EFV+ABC/3TC	Yes[a]
RPV/TDF/FTC	Yes[b]
RPV+ABC/3TC	Yes[a]
EFV+ZDV/3TC	No
NVP+TDF/FTC or ZDV/3TC	No
NVP+ABC/3TC	Yes[a]
RPV+ZDV/3TC	Yes[b]

3TC: lamivudine; ABC: abacavir; EFV: efavirenz; FTC: emtricitabine; NNRT: non-nucleoside reverse transcriptase inhibitor; RAL: raltegravir; RPV: rilpivirine; TDF: tenofovir; ZDV: zidovudine
[a]ABC should be used with caution in patients with pretreatment HIV RNA >100,000 copies/ml
[b]RPV should be used with caution in patients with pretreatment HIV RNA >100,000 copies/ml

Table 2: Baseline Virologic Load Consideration by DHHS Regimen [8].

combination Complera™ [10], provide additional ARV therapeutic options for patients and healthcare providers. However, these drugs do not yet have extensive clinical exposure or concomitant patient-years of experience across broad spectrums of patient populations. NNRTI-based regimens that are currently recommended by the DHHS guidelines (October 14, 2011) and their baseline HIV RNA level precautions are noted in table 2.

ARV therapeutic decisions must be made in consideration of available treatment guidelines and a number of individual patient- and disease-specific factors [8]. These include drug tolerability, potential for drug-drug interactions, baseline VL and resistance-testing results, comorbidities and/or coinfections, as well as other considerations [8]. For example, depending on socioeconomic factors, a patient's access to healthcare, medical or prescription cost coverage, and out-of-pocket drug costs are factors that can influence treatment decisions as well. Also, in recent years, several established ARVs have become available in generic formulation, and other agents (such as the NNRTIs, NVP, and EFV) will become available in generic form over the next few years. Such options may give patients and providers additional lower-cost avenues to consider when constructing ARV regimens [15].

Conclusions

Clinical experience has taught us that ARV regimens are generally not as effective in HIV infected patients with high VLs, i.e., those with >100,000 copies/ml. Specific examples are listed in table 2. It should be noted that both ABC and RPV include precautions in their patient labels regarding use of these drugs in patients with high VL [2,16]. These concerns are also noted in the latest edition of the DHHS guidelines [8], which indicate that recommended regimens incorporating either ABC or RPV should be used with caution in patients with high VL [8]. Newer regimens with reduced pill counts and/or once-daily dosing strategies have been shown to improve adherence (especially in homeless and marginally housed patients), leading to greater virologic efficacy and safety [11]. In conclusion, numerous patient and viral factors should be considered during regimen selection and individualization, including HIV VL and regimen responses under these conditions.

Acknowledgement of Financial Support

Editorial and writing assistance was provided by José L. Walewski, PhD, of Envision Scientific Solutions, which was contracted by BIPI for these services. The author meets the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and was fully responsible for all content and editorial decisions, and was involved at all stages of manuscript development.

As a contract investigator CB was compensated for her time and resources used to enroll patients at her study site, and to gather data per study protocol. The author received no direct compensation for her role in developing this manuscript.

References

1. National Institute of Allergy and Infectious Diseases (NIAID) (2011) Factors that Affect Disease Progression.
2. EDURANT (2011) Rilpivirine. Tibotec Pharmaceuticals, Raritan NJ, USA.
3. Van Leth F, Andrews S, Grinsztejn B, Wilins E, Lazanas MK, et al. (2005) The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. AIDS 19: 463-471.
4. Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, et al. (2009) Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 361: 2230-2240.
5. Smith KY, Patel P, Fine D, Bellos N, Sloan L, et al. (2009) Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 23: 1547-1556.
6. Cozzi-Lepri A, Paredes R, Phillips A, Lazzarin A, Van Lunzen J, et al. (2011) Predictors of virologic response to etravirinebased cART regimens in a large European cohort of HIV-infected patients. 18th Conference on Retroviruses and Opportunistic Infections (CROI) Boston, MA, USA.
7. Taiwo B, Zheng L, Gallien S, Matining RM, Kuritzkes TR, et al. (2011) Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). AIDS 25: 2113-2122.
8. Department of Health and Human Services (2011) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.
9. Gathe J, Andrade-Villanueva J, Santiago S, Horban A, Nelson M, et al. (2011) Efficacy and safety of nevirapine extended-release once daily versus nevirapine immediate-release twice-daily in treatment-naive HIV-1-infected patients. Antivir Ther 16: 759-769.
10. COMPLERA (2011) Eemtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Tablets. Gilead Sciences Inc, Foster City, CA, USA.
11. Bangsberg DR, Ragland K, Monk A, Deeks SG (2010) A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. AIDS 24: 2835-2840.
12. Viramune (2011) Nevirapine. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT, USA.
13. Rodriguez-Arrondo F, Aguirrebengoa K, Portu J, Munoz J, Garcia MA, et al. (2009) Long-term effectiveness and safety outcomes in HIV-1-infected patients after a median time of 6 years on nevirapine. Curr HIV Res 7: 526-532.
14. Soriano V, Arasteh K, Migrone H, Lutz T, Opravil M, et al. (2011) Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. Antivir Ther 16: 339-348.
15. Purdum AG, Johnson KA, Globe DR (2004) Comparing total health care costs and treatment patterns of HIV patients in a managed care setting. AIDS Care 16: 767-780.
16. Daily Med (2011) EPZICOM (abacavir sulfate and lamivudine). GlaxoSmithKline, Research Triangle Park, NC, USA.